correlation to treatment in any whole organism (such as humans). Applicants respectfully traverse this ground of rejection.

Historically, *In re Krimmel*, 292 F.2d 948 (CCPA 1961), the court found that even if applicant's claimed invention was for treatment of humans, lack of proof of effectiveness in humans was not determinative of the patentability. It was stated therein:

> [t]here is nothing in the patent statute or any other statutes called to our attention which gives the Patent Office the right or the duty to require any applicant to prove that compounds or other materials, which he is claiming, and which he has stated are useful for 'pharmaceutical applications' are safe, effective and reliable for use with humans.

More importantly, *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995), the CAFC explicitly stated the Commissioner "confuses the requirement under the law for obtaining a patent with the requirement for obtaining government approval to market a particular drug for human consumption", and the utility question was couched as a rejection under §112, 1st ¶ not §101. It is respectfully submitted that the Patent Office must not impose an unreasonably high standard of proof for applicants to establish therapeutic utility.

Moreover, one skilled in the art at the time the invention was made would not be required to practice undue experimentation to make and use the claimed therapeutic agent. There are numerous teachings referring to clinical trials of anthracyclines, which use in chemotherapy is well documented and appreciated by one skilled in the art. For example, in Schwonzen M, et al., "Liposomal doxorubicin and weekly paclitaxel in the treatment of metastatic breast cancer", Anticancer Drugs 2000 Oct; 11(9):681-5 it is mentioned:

> [t]he combination of paclitaxel and doxorubicin or epirubicin is highly active against metastatic breast cancer, yet may produce congestive heart failure. Liposome-encapsulated doxorubicin is a new formulation of doxorubicin with no dose-limiting cardiac toxicity. Twenty-one patients with metastatic breast cancer were treated with pegylated liposomal doxorubicin (20 mg/m2, day 1) and paclitaxel (100 mg/m2, days 1 and 8) for six cycles every 2 weeks. All patients had had relapse or progression on one to five previous chemotherapies. We observed two patients with complete and eight patients with partial remissions (48% response rate). Eight of the 10 responders had had previous therapy with epirubicin, doxorubicin or mitoxantrone. The mean remission duration was 5 months. Disease progression due to brain metastasis occurred in five cases. Severe side effects (grade 3 WHO) were alopecia (100%), skin toxicity in 29%, neuropathy in 24% and mucositis in 13%. Leukopenia (grade 4 WHO) was observed in 48%, but there was no cardiac toxicity, no death and no hospitalization. The combination of weekly paclitaxel and liposomal doxorubicin every 2 weeks is highly effective in previously treated patients. Based on the doses we administered, we recommend 15 mg/m2 liposomal doxorubicin every 2 weeks and 80 mg/m2 paclitaxel weekly.

Therefore, Applicants believe structurally similar compounds, which have been proven, in vivo, have been effective as chemotherapeutic agents against various tumor models. As supported, *In re Brana*, supra, Applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of §112. Withdrawal of the §112, 1st ¶ is respectfully requested.

CONCLUSION

Applicants respectfully request reconsideration and allowance of all claims. If the Examiner has any questions or other correspondence regarding this application, Applicants request that Examiner contact the Applicants' attorney at the change of correspondence at the below-listed telephone number and overseas address. It is believed no additional fees are required to be paid at this time, however, in the event any other fee is due,

authorization to charge deposit account no. 50-2497 (Attorney Docket No. 32144183-001336) is provided.

Attached hereto is a *marked-up* version of the changes made to the claims by the current amendment. The attached page is captioned **VERSION WITH MARKINGS TO SHOW CHANGES MADE.**

Favorable action is respectfully requested.

Respectfully submitted,

BAKER & McKENZIE

YUN, Caroline Joo
Reg. No. 34,952

December 4, 2002
Caroline J. Yun
BAKER & McKENZIE
14th Floor, Hutchison House
10 Harcourt Road, Central
Hong Kong SAR
(852) 2846 1800 (general)
(852) 2846 2453 (direct)
(852) 2845 0476 (facsimile)
caroline.j.yun@bakernet.com (email)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The amendments to the claims are illustrated below with boldfaced underlined text representing what has been added and boldfaced bracketed text representing what has been deleted.

IN THE CLAIMS

8. (Amended) ~~A method for inhibiting the proliferation of liver cancer comprising the steps of:~~

~~(a) administering to a subject in need of such therapy an effective amount of a composition containing doxorubicin encapsulated in desialyated glycoprotein α 1 coupled to a liposome; and~~

~~(b) delaying a cell division of cells.~~

~~Please add the following new claim 9.~~

10. (New) **A method for preparing a therapeutic agent to a tissue expressing asialoglycoprotein receptors comprising delivery to the tissue an effective amount of the agent encapsulated in a liposome having a molar PC:Chol:PS ratio 11:4:0.025 coupled to desialyated glycoprotein α 1 by an avidin-biotin or thiol-maleamide linkages.**